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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/060,087	01/31/2002	Donna Mendrick	044921-5038-01	6811

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EXAMINER	
LY, CHEYNE D	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 08/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S/M

Office Action Summary	Application No.	Applicant(s)	
	10/060,087	MENDRICK ET AL.	
	Examiner	Art Unit	
	Cheyne D Ly	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60-74 and 88-110* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *60-74 and 88-110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *60-74 and 88-110* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/18/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' arguments filed March 15, 2004 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. The header of pages 2-11, filed March 15, 2004, has been amended to recited "10/060,087".

3. Applicant's summary of the telephone interview on November 06, 2003 has been acknowledged.

4. The addition of claims 93-110 has been acknowledged.

5. Claims 60-74 and 88-110, alpha-naphthylisothiocyante (ANIT), are examined on the merits.

IDS

6. The reference number 51 listed in the IDS, filed October 18, 2002, has not been considered due to said reference not having a publication date and not being present in the file of the instant application or parent application.

CLAIM REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 88-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. This rejection is necessitated by Applicant's amendments.

10. Specific to claim 88, lines 1-2, said claim recites "using...of claim 60 to predict a toxic response in a cell or tissue sample" which causes said claim to be vague and indefinite because claim 60, step (b), is directed to "liver cell or tissue." Claim 88 is unclear as to whether the method is directed to a generic type of cell or tissue, or a specific liver cell or tissue. Clarification of the metes and bounds is required. Claims 89-92 are rejected for being dependent from claim 88.

CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 60-74 and 88-110 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. NEW MATTER REJECTION.

13. This rejection is necessitated by Applicant's amendments.

14. Specific to claim 60, lines 2-4 and 7, and claim 98, lines 2-4 and 6, the limitation of "a liver cell or tissue sample" has not been found in the pointed to support. It is noted that the

pointed support discloses a generic tissue or cell sample (page 32, [0137] and [0138]), which is different from the limitation of "a liver cell or tissue sample". Claims 61-74 and 99-110 are rejected for being dependent from claim 60 or 88.

15. Specific to claims 95-97, the limitations of "at least 10 genes", "at least 50 genes", and "at least 100 genes" of tables 3A-DD have not been found in the pointed to support. It is noted the pointed to support discloses "expression levels of about...from Tables 1-3" in page 16, [0070]. The tables recited in the instant claims are different from those disclosed in the specification. Further, the limitation of "at least" in the claims is different from "about" in the specification.

CLAIM REJECTIONS - 35 USC § 101

16. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

17. Claims 60-74 and 93-110 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory algorithm type subject matter.

18. This rejection is maintained with respect to claims 60-74, as recited in the previous office action mailed October 15, 2003. The instant rejection has been extended to new claims 93-110.

19. This rejection is necessitated by Applicant's amendments.

RESPONSE TO ARGUMENTS

20. Applicant argues that amended claims 60 and 98 recite limitations which cause said claims to be of statutory subject matter. Applicant argument has been fully considered and found to be unpersuasive as discussed below.

21. Claims 60-74 and 93-110 are rejected because said claims are directed to a computer system and readable medium comprising algorithmic steps for quantifying gene expression data without any physical alteration step, which is considered to be non-statutory subject matter. "For example, a computer process that simply calculates a mathematical algorithm that models noise is nonstatutory. However, a claimed process for digitally filtering noise employing the mathematical algorithm is statutory." (MPEP § 2106 (IV)(B)(2) (b), part ii). Similar to the nonstatutory example above, the instant invention comprises algorithmic steps for quantifying gene expression data without any physical alteration resulted from said analysis or modeling steps. It is acknowledged that the instant invention comprises algorithmic steps for quantifying gene expression data, however, said steps do not cause any physical outside of the computer system or readable medium as a result of said quantifying steps. Therefore, "such activity is not determinative of whether the process is statutory because such transformation alone does not distinguish a statutory computer process from a nonstatutory computer process" (MPEP § 2106 (IV)(B)(2) (b), part ii).

CLAIM REJECTIONS - 35 USC § 103

22. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

23. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

24. Claims 60-74, 88-94, and 98-110 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friend et al. (US 6218122 B1) taken with Cunningham et al. (US 6372431 B1).

25. This rejection is maintained with respect to claims 60-74, 88-92, as recited in the previous office action mailed October 15, 2003. The instant rejection has been extended to new claims 93, 94, and 98-110.

26. This rejection is necessitated by Applicant's amendments.

RESPONSE TO ARGUMENTS

27. Applicant argues that Friend et al. does not disclose or suggest a database, or a computer system containing a database, of animal liver gene expression levels containing toxin-exposed and control excipient-exposed samples that can be used to predict a toxic effect of a test compound or hepatotoxicity resulting from exposure to a test compound. Applicant argues that the cited reference does not disclose comparing gene expression levels, or a profile of gene expression levels, obtained from a sample exposed to a test compound to control excipient-exposed samples, or a profile of control samples, to predict a toxic effect of a test compound or hepatoxicity resulting from exposure to a test compound. Additionally, Applicant argues that the reference also provides no guidance for developing the database, or

the computer system containing the database, of the instant invention or for predicting toxicity according to the methods of the instant invention. Applicant has also directed the above arguments to Cunningham et al.

28. Applicant's arguments as directed to Friend et al. and Cunningham et al. have been fully considered and found to be unpersuasive as discussed below.

29. Friend et al. discloses a computer system and database to be used in a method for monitoring toxic effects of a therapy (e.g., one or more drugs or a chemotherapy) (column 3, lines 47-65) as directed to disease markers (column 14, lines 18-19). The data captured in said database comprises of expression level of specific gene transcripts of cells wherein said cells having been exposed to a drug of interest (column 21 lines 10-17 and Table 2). The data captured from a single cell is compared to those of therapy-exposed or diseased cell and an untreated or non-diseased cell (control) (column 22, lines 31-35). Further, the method of Friend et al. is directed to using said computer system and database to monitor changes in cells in the body such as in the liver (column 1, lines 55-62) for defining a "signature" of the particular alterations which are correlated (predict) with the progression of the particular disease state or therapy (column 2, line 60, to column 3, line 1).

30. It is noted that the instant claims do not recite any limitations such as "guidance for developing the database, or the computer system containing the database". However, the disclosure of Friend et al. for data captured in said database comprises of expression level of specific gene transcripts of cells wherein said cells having been exposed to a drug of interest is consistent with the limitation of said database and computer system of the instant claimed invention.

31. Therefore, the citation of Friend et al. above and re-iterated below sufficiently support that Applicant's argument and claims amendment have not overcome the instant rejection.

REJECTION RE-ITERATRED

32. Friend et al. discloses a computer system and database to be used in a method for monitoring toxic effects of a therapy (e.g., one or more drugs or a chemotherapy) (column 3, lines 47-65) as directed to disease markers (column 14, lines 18-19). The data captured in said database comprises of expression level of specific gene transcripts of cells wherein said cells having been exposed to a drug of interest (column 21 lines 10-17 and Table 2). The data captured from a single cell is compared to those of therapy-exposed or diseased cell and an untreated or non-diseased cell (control) (column 22, lines 31-35), as in instant claims 61, 62, 67, 99, 100, 103, and 107.

33. The method of Friend et al. is directed to using said computer system and database to monitor changes in cells in the body such as in the liver (column 1, lines 55-62) for defining a "signature" of the particular alterations which are correlated (predict) with the progression of the particular disease state or therapy (column 2, line 60, to column 3, line 1). The analytic embodiments for the data comparison are performed by computer software (columns 18-20, §5.3.3), as in instant claims 60, 69, 71, and 105.

34. Table II (column 11) displays information directed to genes wherein the expression levels are up- or down-regulated to exemplify the partial disruption of even a single protein within a cell, such as by exposure to a drug (toxin as directed to side effects) (column 10, lines 28-36), as in instant claim 88.

35. The method of Friend et al. discloses that expression profiles were established for approximately 6000 genes (column 10, lines 40-42). The differential expression of the 6000 genes exposed to a drug (column 11, lines 40-45). The diagnostic expression profile can be compared with the perturbation response curves to find the best-fit over all possible values (column 13-18, § 5.3); wherein the comparison is implemented in said computer and database (column 18, § 5.3.3), as in claims 89-92.

36. The method and system of Friend et al is directed to a plurality of toxins (column 12, lines 18-30), as in instant claims 63 and 101.

37. The above cited method which uses the computer system comprising a database stored on computer readable medium (column 34, claim 48), as in instant claims 94 and 98.

38. However, Friend et al. does not disclose that the toxin is an ANIT or an external database such as GenBank.

39. Cunningham et al. discloses a method for screening compounds and therapeutics for metabolic responses indicative of a toxic compound or molecule (Abstract) such as hepatotoxin (column 7, line 43-50). The toxic compounds may include ANIT affecting the liver (column 2, lines 1-8), as in instant claims 72, 93, and 108

40. Tables 1-10 disclose differential expression of genes correlated to liver pathology, as in claims 70, 74, 106, and 110.

41. The fluorescence signal within each element was then integrated to obtain a numerical value corresponding to the average intensity of the signal (column 24, lines 15-19), as in instant claims 66 and 102.

42. The method of Cunningham et al. comprises performing toxicity tests on rats plus one control group (column 17, lines 25-32); using the GenBank database for verifying the gene markers (column 21, lines 24-59) and the discriminant scores are disclosed in Table 1, as in instant claim 64, 65, 68, 73, 104, and 109.

43. Friend et al. discloses an improvement for monitoring toxic effects of a therapy, which would result in more effective therapeutic treatments and significant benefit to patience (column 2, lines 16-31). While, Cunningham et al. discloses a type of treatment wherein toxicological effects are monitored as directed to a therapy (Abstract etc.). Therefore, the improvement disclosed by Friend et al. is directly applicable to the invention of Cunningham et al.

44. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated to partake the improvement disclosed by Friend et al. to utilize a type of treatment wherein toxicological effects are monitored as directed to a therapy (Abstract etc.), as taught by Friend et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use a type of treatment wherein toxicological effects are monitored as directed to a therapy as taught by Friend et al. and Cunningham et al.

CONCLUSION

45. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

46. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

47. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

48. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

49. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

50. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (571) 272-0716. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

51. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (571) 272-0722.

C. Dune Ly
8/11/04